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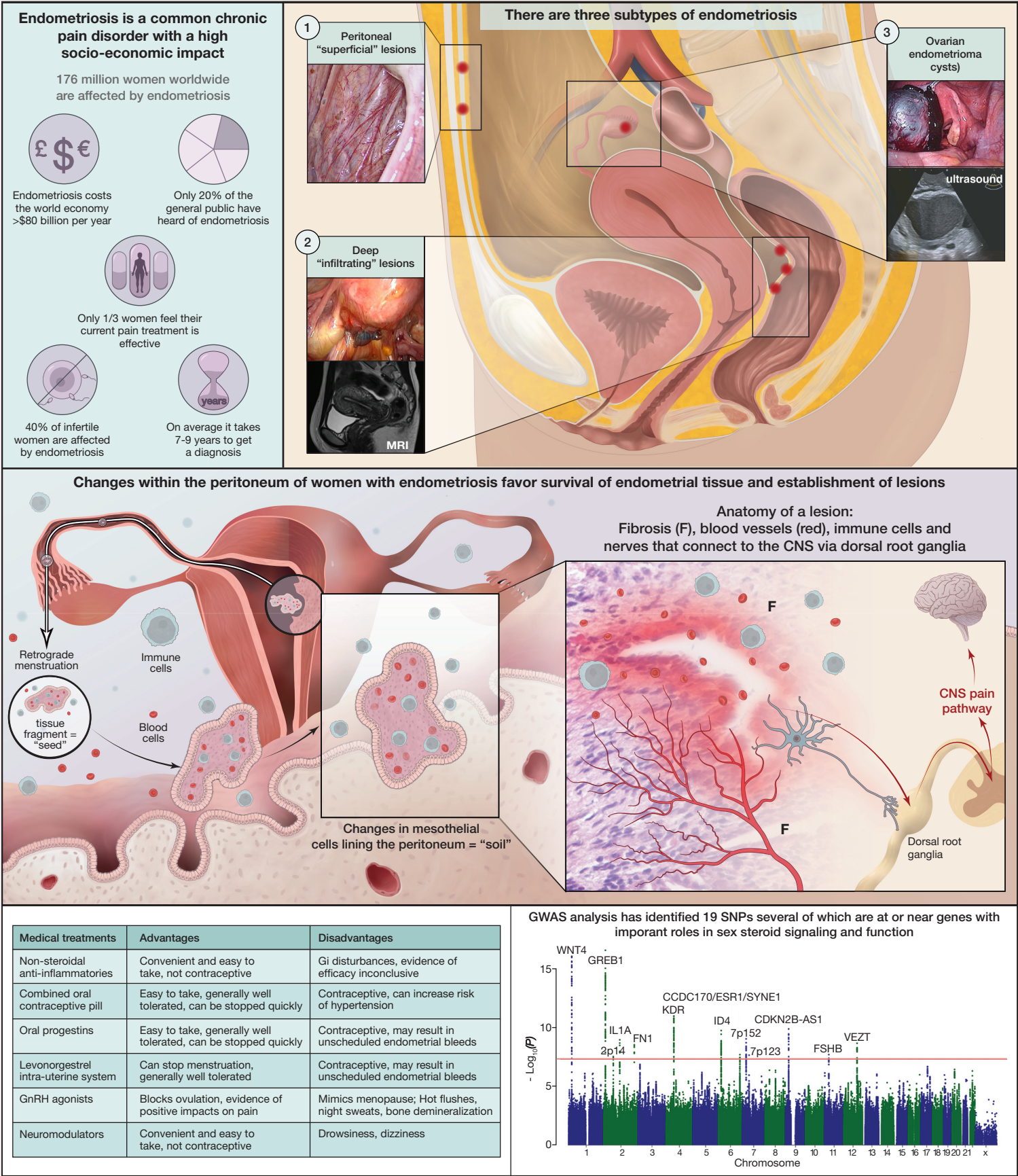
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Endometriosis is a chronic, estrogen-dependent, neuroinflammatory condition that is associated with pelvic pain. It affects an estimated 176 million women worldwide (~10% of women of reproductive age). While the socioeconomic impact of endometriosis is high (~80 billion USD, >70 billion euros per year), awareness among public and health care practitioners is low relative to disorders with similar prevalence and societal burden, e.g., diabetes (Horne et al., 2017).

Clinical Phenotypes, Symptoms, Comorbidities and Natural History

Endometriosis is defined by the presence of endometrial-like tissue ("lesions") outside the uterus. Three subtypes of endometriosis are described: superficial peritoneal, ovarian (endometrioma cysts), and deep (infiltrating) (Johnson et al., 2017). It is estimated that 50%–60% of women with chronic pelvic pain have endometriosis, but there is poor correlation between pain severity and the amount, location, and subtype of endometriotic lesions, with some women being asymptomatic. Women with endometriosis are at higher risk of infertility; ovarian, endometrial, and breast cancers; melanoma; asthma; and autoimmune and cardiovascular disease (Kvaskoff et al., 2015). The natural history of the disease is uncertain. It is not known whether superficial peritoneal disease can progress to become another subtype and whether disease progression (or lack of treatment) can lead to worsening symptoms. Genetic, hormonal, anatomical, and immunological factors are all implicated in the formation and development of endometriotic lesions.

Diagnosis and Clinical Management

There are no accurate non-invasive biomarkers of endometriosis. As definitive diagnosis requires surgery, there is often a long diagnostic delay after onset of symptoms (~7–9 years). Ovarian and deep endometriosis subtypes may be identified on imaging (e.g., ultrasound or MRI). Current treatment options for endometriosis are largely inadequate. Medical treatments mostly reduce circulating estrogen concentrations and, hence, may induce menopausal-like symptoms and lead to bone demineralisation. Surgical treatments aim to excise or ablate all visible disease, but persistence/recurrence rates of endometriosis after surgery are as high as 20% after 2 years and 40%–50% after 5 years.

Genetics

Twin studies report the heritable component of endometriosis as ~50%. Large-scale genome-wide association studies (GWASs) have been conducted, with new insights gained by pooling data in meta-analyses: recent findings have identified at least 19 independent SNPs significantly associated with endometriosis, some of which appear associated with genes implicated in steroid hormone signaling (Sapkota et al., 2017). Cross-disease GWAS meta-analysis identified 13 distinct loci associated with both endometriosis and endometrial cancer, complementing the epidemiological evidence of an association. In addition, a recent study detected somatic cancer driver mutations in cells in deep endometriotic lesions (Anglesio et al., 2017).

Survival of Endometrial Tissue and Establishment of Endometriosis Lesions: An Example of "Seed and Soil"?

Reflux of endometrial tissue fragments/cells and protein-rich fluid through the fallopian tubes into the pelvis during menstruation is considered the most likely explanation for why endometriotic lesions form within the peritoneal cavity. Studies exploring why lesions develop in some, but not all, women have detected changes in the endometrial tissue (the "seed") as well as the peritoneal fluid and cells lining the cavity (the "soil"). Analysis of eutopic endometrium from women with endometriosis has identified altered expression of genes implicated in the inflammation/immune response, angiogenesis, and steroid responsiveness (progesterone "resistance") (McKinnon et al., 2018). Shed menstrual tissue contains high concentrations of pro-inflammatory cytokines, proteases, and immune cells, all of which may influence the peritoneal microenvironment after reflux. Stem/progenitor cells have been identified in the endometrium and are thought to survive and implant onto the peritoneum, contributing to lesions (Cousins et al., 2018). Mesothelial cells line the pelvic peritoneal cavity and cover the surface of the ovary, and changes in their function in women with endometriosis including altered morphology, metabolism (switch to aerobic glycolysis) (Horne et al., 2019), and production of factors that promote immune cell recruitment and angiogenesis are all thought to favor survival and establishment of lesions (Young et al., 2013). Physiological hormonal fluctuations in women induce cyclical episodes of cell proliferation, inflammation, injury, and repair within lesions that favor fibroblast to myofibroblast differentiation and fibrosis.

Mechanisms Contributing to Endometriosis-Associated Pain

The development of a new blood supply and associated nerves (neuroangiogenesis) are considered key to the establishment of endometriotic lesions and activation of peripheral pain pathways. Sensory C, sensory Aδ, cholinergic, and adrenergic nerve fibers have all been detected in lesions. Estrogens can promote cross-talk between immune cells and nerves within lesions, increasing expression of nociceptive ion channels such as TRPV1 (Greaves et al., 2015). Factors that promote inflammation and nerve growth, such as NGF, TNF α , and IL1 β , are increased in the peritoneal fluid of women with endometriosis and may exacerbate a neuroinflammatory cascade. Endometriosis-associated chronic pelvic pain is associated with alterations in the CNS of women, including changes in the volume of regions of the brain and in brain chemistry (As-Sanie et al., 2012).

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